PATENT COOPERATION TREATY

PCT

Rec'd PCT/PTO 12 MAY 2005

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MC-009-015	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IN 03/00358	International filing date *(day/month/year)* 14.11.2003	Priority date *(day/month/year)* 15.11.2002
International Patent Classification (IPC) or both national classification and IPC C07D239/91		
Applicant CADILA HEALTHCARE LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.06.2004	17.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Scruton-Evans, I Telephone No. +49 89 2399-8272

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 03/00358

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-88	as originally filed

Claims, Numbers

3-8, 10-12, 14-22	as originally filed
1, 2, 9, 13	received on 14.12.2004 with letter of 11.12.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 17-21,1-5,7,8,14-22(partly)

   because:

   ☒ the said international application, or the said claims Nos. 17-21 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-5,7,8,14-22(partly)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	6,11
	No:	Claims	1-5,7-10,12-22
Industrial applicability (IA)	Yes:	Claims	1-16,22
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 17-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

As was stated in the PCT/ISA/210, only those compounds wherein A is a heterocycle, Ar is 1,4-phenylene and X is O as well as all of the examples was searched, due to a lack of support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT. This written opinion is thus limited to the searched subject matter.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the search report are referred to in this communication;

D1: WO 91/19702 A (PFIZER) 26 December 1991 (1991-12-26)

D2: EP-A-0 930 299 (JAPAN TOBACCO INC) 21 July 1999 (1999-07-21)

D3: EGBERTSON M S ET AL: "NON-PEPTIDE FIBRINOGEN RECEPTOR ANTAGONISTS. 2. OPTIMIZATION OF A TYROSINE TEMPLATE AS A MIMIC FOR ARG-GLY-ASP" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 16, 1994, pages 2537-2551, XP000574969 ISSN: 0022-2623

D4: JP 51 149265 A (YOSHITOMI PHARMACEUT IND LTD) 22 December 1976 (1976-12-22)

D5: EP-A-0 478 363 (MERCK & CO INC) 1 April 1992 (1992-04-01)

D6: WO 96/38415 A (SUMITOMO METAL IND ;TAKENO HIDEKAZU (JP); IKEMOTO TOMOYUKI (JP); S) 5 December 1996 (1996-12-05)

D7: WO 01/40170 A (ASTRAZENECA AB ;FAEGERHAG JONAS (SE); LI LANNA (SE); LINDSTEDT ALS) 7 June 2001 (2001-06-07)

With regard to the requirement for novelty, the introduction of the provisos into the

claims 1 and 9 and the deletion of the possibility of NR1R2 for G1 appears to have resulted in claims satisfying the requirements of Article 33(2) of the PCT.

With regard to the requirement for inventive step (Article 33(3) of he PCT), the compounds of formula I and IIIa of the present application are described as being inter alia antidiabetic, hypolipidaemic and hypocholesterolemic. D1 and D2 are considered to represent the closest prior art for the compounds of formula IIIa, D1 differing only in the fact that one of the substituents on A is heteroaryl or heteroaromatic, and re D2 only in the nature of G1 . It has been argued in your reply that minor modifications in core structure lead to changes in pharmacological profiles, and that the compounds are a non-obvious solution to the problem of providing further novel compounds with the desired activities. Whilst this could be accepted as evidence of inventive step, it could only justify the acknowledgement for the prepared and tested examples, together with a reasonable generalisation thereof, as by the admissions of the Applicant, the effect of minor modifications cannot be predicted. The same argument must apply to the compounds of formula I, for which D7 is considered to be the closest prior art. In conclusion, an inventive step could be acknowledged for the searched examples which have been prepared and tested, and a reasonable generalisation thereof, considered to be represented by claims 6 and 11, but no conclusion can be drawn from your arguments with respect to the generalisations of the other claims.

For the assessment of the present claims 17-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

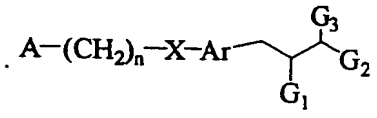
Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*

WO2004031162	15.04.2004	06.10.2003	07.10.2002
WO02/092084	21.11.2002	06.05.2002	15.05.2001
WO2004004665	15.01.2004	02.07.2003	09.07.2002
WO03/072102	04.09.2003	13.02.2003	25.02.2002

We claim:

1. A compound of the general formula (I),



(I)

their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, wherein

'A' represents a substituted or unsubstituted, group selected from aryl, heteroaryl, heterocyclyl groups; 'n' is an integer from 1-3, with the proviso that when A is substituted or unsubstituted phenyl group, then Ar does not represent a divalent phenyl group; 'X' represents oxygen or sulfur;

'Ar' represents a substituted or unsubstituted single or fused divalent aromatic, heteroaromatic or a heterocyclic group;

G_1 represents OR_1, SR_1, $S(O)R_3$, $S(O)_2R_3$, N_3, CN, COOH, tetrazolyl groups; G_2 represents OR_1, NR_1R_2, SR_1, $S(O)R_3$, $S(O)_2R_3$, N_3, CN, COOH, tetrazolyl groups; R_1, R_2 represents hydrogen, substituted or unsubstituted groups selected from linear or branched $(C_1$-$C_8)$alkyl, $(C_3$-$C_7)$cycloalkyl, acyl, aryl, heteroaryl, heterocyclyl, aminocarbonyl, aralkyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, heteroarylaminocarbonyl, heteroaralkylaminocarbonyl, heterocyclylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaraloxycarbonyl, heterocycloxycarbonyl groups; R_3 represents substituted or unsubstituted groups selected from alkyl, aryl, polyhaloalkyl, heterocyclyl, heteroaryl groups; *with the proviso that, when G_2 represents NR_1R_2, G_1 does not represent –OH group;* G_3 represents hydrogen or $(C_1$-$C_8)$alkyl or $(C_3$-$C_7)$cycloalkyl groups.

2. A compound as claimed in claim 1 wherein the substitutents on 'A', R_1, R_2 & R_3 may be same or different and are independently selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl,

aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives; .

3. A compound as claimed in claim 1 wherein, suitable substituents on any substituent of 'A' may be same or different and are independently selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives, phosphonic acid and its derivatives.

4. A compound as claimed in claim 1 wherein 'Ar' represents a substituted or unsubstituted single or fused aromatic or heteroaromatic or heterocyclic group.

5. A compound according to claim 1, wherein the substituents on the group represented by 'Ar' represents substituted or unsubstituted linear or branched alkyl, alkoxy, thioalkyl, halogen, haloalkyl, haloalkoxy, acyl, amino, acylamino, thio or carboxylic or sulfonic acids and their derivatives, phosphonic acid and their derivatives.

6. The compounds as claimed in claim 1, selected from

3-(6-Benzyloxy-naphthalen-2-yl)-2-ethoxy-propan-1-ol;

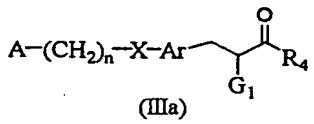
(2S)-Ethoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propan-1-ol;

(2S)-Ethoxy-3-{4-(4-hydroxy-3-methyl-3,4-dihydro-quinazolin-2yl-methoxy)-phenyl}-propan-1-ol;

2-Hydroxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propan-1-ol;

3-{4-[2-(2,3-Dihydro-benzo[1,4]thiazin-4-yl)-ethoxy]-phenyl}-(2S)-ethoxy-propan-1-ol;

.9. Novel compounds of formula (IIIa), , their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, wherein 'A' represents 4-oxazolyl group substituted with one or two substitutents selected from substituted or unsubstituted linear or branched (C_1-C_{12})alkyl, substituted or unsubstituted single or fused heteroaryl or heterocyclic groups with the proviso that one of the substituents on "A" is always a heteroaryl or heterocyclic group and with the further proviso that when the heteroaryl is pyridyl group, such group is unsubstituted; ; 'Ar' represents unsubstituted phenyl; G_1 represents OR_1 or SR_1 where R_1 represents hydrogen, perfluoro(C_1-C_{12})alkyl, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, cyclo(C_1-C_{12})alkyl, aryl, ar(C_1-C_{12})alkyl, heteroaryl, heteroar(C_1-C_{12})alkyl, heterocyclyl, alkoxyalkyl, aryloxyalkyl, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl or acyl groups; R_4 represents OH, alkoxy or aryloxy, aralkoxy or NR_1R_2 groups, where R_1 & R_2 may be same or different and independently represent hydrogen, substituted or unsubstituted groups selected from linear or branched (C_1-C_8)alkyl, (C_3-C_7)cycloalkyl, acyl, aryl, heteroaryl, heterocyclyl, aminocarbonyl, aralkyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, heteroarylaminocarbonyl, heteroaralkylaminocarbonyl, heterocyclylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaraloxycarbonyl, heterocycloxycarbonyl groups or SO_2R_3 wherein R_3 represents substituted or unsubstituted groups selected from alkyl, aryl, polyhaloalkyl, heterocyclyl, heteroaryl groups; 'n' is an integer from 1-3; X represents O or S,



(IIIa)

10. The compounds as claimed in claim 9, wherein the substitutions on the substituents on 'A' are selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and

(2S)-Ethoxy-3-(4-{2-[5-methyl-2-(5-bromo-thiophen-2-yl)-oxazol-4-yl]-ethoxy}-phenyl)- propanoic acid and its pharmaceutically acceptable salts;

(2S)-Ethoxy-3-(4-{2-[5-methyl-2-(5-methyl-furan-2-yl)-oxazol-4-yl]-ethoxy}-phenyl)-propanoic acid and its pharmaceutically acceptable salts;

2(S)-Ethoxy-3-[4-(5-methyl-2-pyridin-2-yl-oxazol-4-ylmethoxy)-phenyl]- propanoic acid and its pharmaceutically acceptable salts;

2(S)-Ethoxy-3-[4-(5-methyl-2-pyridin-4-yl-oxazol-4-ylmethoxy)-phenyl]- propanoic acid and its pharmaceutically acceptable salts;

2(S)-Ethoxy-3-[4-(5-methyl-2-pyridin-3-yl-oxazol-4-ylmethoxy)-phenyl]- propanoic acid and its pharmaceutically acceptable salts;

12. The compounds as claimed in claims 9-11, suitable as intermediates for the preparation of compounds of formula (I).

13. A process for the preparation of compound of formula (IIIa) as claimed in any one of claims 9 to11 comprising

i. reacting a compound of formula (IVa) wherein 'A' represents 4-oxazolyl group substituted with one or two substitutents selected from substituted or unsubstituted linear or branched (C_1-C_{12})alkyl, substituted or unsubstituted single or fused heteroaryl or heterocyclic groups with the proviso that one of the substituents on "A" is always a heteroaryl or heterocyclic group and with the further proviso that when the heteroaryl is pyryl group, such group is unsubstituted; ; 'n' is an integer from 1-3; and 'L' represents a leaving group selected from halogen, mesylate, tosylate & triflate, with a compound of formula (Vc) wherein X represents oxygen or sulfur; 'Ar' represents unsubstituted phenyl; G_1 represents OR_1 or SR_1, where R_1 represents hydrogen, perfluoro(C_1-C_{12})alkyl, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, cyclo(C_1-C_{12})alkyl, aryl, ar(C_1-C_{12})alkyl, heteroaryl, heteroar(C_1-C_{12})alkyl, heterocyclyl, alkoxyalkyl, aryloxyalkyl, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl or acyl groups; R_4 represents OH, alkoxy or aryloxy, aralkoxy or NR_1R_2 groups, where R_1 & R_2 may be same or different and independently represent hydrogen, substituted or unsubstituted groups selected from linear or branched (C_1-C_8)alkyl, (C_3-C_7)cycloalkyl, acyl, aryl, heteroaryl, heterocyclyl, aminocarbonyl, aralkyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, heteroarylaminocarbonyl, heteroaralkylaminocarbonyl, heterocyclylaminocarbonyl,

alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heteroaryloxycarbonyl, heteroaraloxycarbonyl, heterocycloxycarbonyl groups or SO_2R_3 wherein R_3 represents substituted or